Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3854	adenovirus and (nuclear localization)	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 15:58
L2	95	adenovirus.ab. and (nuclear localization)	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 15:58
L3	0	l2 and chimer	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 15:58
L4	20	l2 and chimer?	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:00
L5	2	adeno? and P22	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:01
L6	0	adeno? and vP22	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:00
L7	0	adeno? and antennaepedia	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:01
L8	24	adeno? and tat	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:04
L9	22	adeno? and tat and fusion	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:04
L10	0	adeno?.ab. and tat and fusion	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:04
L11	0	adeno?.ab. and tat and chimer?	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:04
L12	0	AAv2?.ab. and tat and chimer?	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:04
L13	0	AAv2?.ab. and tat	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:05
L14	12	rep.ab. and tat	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:10
L15	2	rep.ab. and vp22	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:10

L16	1	rep.ab. and antennaepedia	US-PGPUB; USPAT; DERWENT	ADJ	ON	2005/11/15 16:10

10/732,813
File 5:Biosis Previews(R) 1969-2005/Nov W1
(c) 2005 BIOSIS
File 155:MEDLINE(R) 1951-2005/Nov 14
(c) format only 2005 Dialog
*File 155: Completed records will cease to update on 16 November. Please see HELP NEWS 154 for details.

Set Items Description
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Set Items Description
S1 6 AAV2 AND FUSION
S2 2 AAV2 AND TAT
S3 0 AAV2 AND VP22
S4 0 AAV2 AND ANTENN?
S5 2 AU='WONG KAMEHAMEHA K'
S6 27 AU='CHATTERJEE SASWATI'
S7 19 S6 AND ADENO?
S8 6 S7 AND FUSION
S9 35 E3-E6
S10 0 S9 AND ADENOVI?
S11 0 S9 AND ADENO?
S12 6 AU='CONRAD JOEL'
S13 0 S12 AND ADENO?
? t s1/7/1-6

1/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0015154145 BIOSIS NO.: 200500061210
Secretion of a TNFR:Fc %%%fusion%%% protein following pulmonary administration of pseudotyped adeno-associated virus vectors
AUTHOR: Sandalon Ziv; Bruckheimer Elizabeth M; Lustig Kurt H; Rogers Linda C; Peluso Richard W; Burstein Haim (Reprint)
AUTHOR ADDRESS: Targeted Genet Corp, 1100 Olive Way,Suite 100, Seattle, WA, 98101, USA**USA
AUTHOR E-MAIL ADDRESS: burstein@targen.com
JOURNAL: Journal of Virology 78 (22): p12355-12365 November 2004 2004
MEDIUM: print
ISSN: 0022-538X _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study evaluated and compared delivery of the tumor necrosis factor alpha receptor (TNFR)-immunoglobulin G1 (IgG1) Fc %%%fusion%%% (TNFR:Fc) gene to the lung by single and repeat administrations of multiple pseudotyped adeno-associated virus (AAV) vectors as a means for achieving systemic distribution of the soluble TNFR:Fc protein. A single endotracheal administration of AAV(2/5)cytomegalovirus (CMV)-TNFR:Fc vector (containing the %%%AAV2%%% inverted terminal repeats and AAV5 capsid) to the rat lung resulted in long-term, high levels of serum TNFR:Fc protein that gradually declined over a period of 8 months. Endotracheal delivery of AAV(2/1)CMV-TNFR:Fc resulted in serum TNFR:Fc protein levels that were detectable for at least 4 months but were 10-fold lower than that of the AAV (2/5) vector. In contrast, secretion

of the TNFR:Fc protein following pulmonary delivery of AAV(2/2)CMV-TNFR:Fc vector was very inefficient, and the protein was detected in the blood only when an airway epithelial cell-specific promoter, CC10, was substituted for the CMV enhancer/promoter to control transgene expression. In the context of AAV(2/5), the CC10 promoter was as efficient as CMV enhancer/promoter in generating similar levels of systemic TNFR:Fc protein, suggesting that this protein is secreted primarily from the airway epithelium. In mice, comparable long-term secretion of TNFR:Fc protein was demonstrated after AAV(2/2) and AAV(2/5) delivery, although the kinetics of transduction appeared to be different. All pseudotyped AAV vectors elicited serum anti-AAV capsid-neutralizing antibody responses, but these did not prevent lung transduction and efficient secretion of TNFR:Fc protein to the circulation following readministration with AAV(2/5). These results highlight the potential utility of AAV vectors containing serotype 5 capsid to deliver and redeliver genes of secreted proteins to the lung to achieve long-term systemic protein expression.

1/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013559564 BIOSIS NO.: 200200153075
Identification of new MHC restriction elements for presentation of the p210 BCR-ABL %%%fusion%%% region to human cytotoxic T lymphocytes (CTL)
AUTHOR: Sun Ji-Yao (Reprint); Chatterjee Saswati; Forman Stephen J (Reprint); Senitzer David (Reprint); Wong K K Jr (Reprint)
AUTHOR ADDRESS: Division of Hematology and Bone Marrow Transplantation, National Medical Center, City of Hope, Duarte, CA, USA**USA
JOURNAL: Blood 98 (11 Part 1): p147a November 16, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001; 20011207
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Chronic myelogenous leukemia (CML) is characterized by a t(9;22) translocation which results in the expression of chimeric, %%%fusion%%% transcripts consisting of cellular bcr and abl genes. BCR-ABL %%%fusion%%% transcripts and corresponding oncoproteins are both necessary for oncogenesis, and are unique to the leukemic cells. Furthermore, the BCR-ABL oncogene %%%fusion%%% region is immunogenic, and several HLA class I and II alleles can present %%%fusion%%% region epitopes to T lymphocytes, generating interest in the potential for the development of CML specific vaccines. Here we report four additional HLA alleles which present %%%fusion%%% region epitopes of the b3a2 splice variant (P210b3a2) of the BCR-ABL oncogene. To elicit anti-BCR-ABL T-cell responses, our studies employed primary human dendritic cells (DC) transduced with a recombinant adeno-associated virus (%%%AAV2%%%) vector encoding a truncated P210b3a2 cDNA fragment containing the %%%fusion%%% region. Two CTL clones generated in this fashion displayed restriction with previously undescribed HLA alleles. The first CTL clone was CD4+ and of the Th1 functional phenotype. Screening a panel of 10 HLA divergent

antigen presenting cell lines demonstrated that this clone was HLA-DRB5*0101 (DR2a) restricted; findings confirmed by anti-HLA-DR monoclonal antibody blocking experiments and demonstration of antigen specific recognition of a cell line into which HLA-DRA and DRB5*0101 were introduced. The minimum cytotoxic epitope (MCE) of the P210b3a2 %%%fusion%%% region binding to DR2a for this clone was identified as FKQSSKALQ, the bolded K representing the new amino acid in the P210b3a2 junction region. Interestingly, this clone could also recognize cells expressing HLA-DRB1*1101 pulsed with a P210b3a2 %%%fusion%%% region peptide. The MCE binding to HLA-DRB1*1101 molecule for this clone is different from FKQSSKALQ. We believe that this is the first description of a single clone recognizing HLA-DRB5*0101 and DRB1*1101. The other BCR-ABL specific CTL clone was CD8+ and HLA-B*3501 and B*3503 restricted, findings similar to those reported by Khanna et al who described a CTL clone that recognized an Epstein Barr virus epitope presented by both B*3501 and B*3503 (Eur J Immunol 1999; 29:1587). To determine whether HLA-DR2a and B35 could present P210b3a2 joining region epitopes via endogenous processing, K562 cells, a leukemic cell line expressing P210b3a2, were transfected with expression plasmids encoding HLA-DR2a, B*3501 or B3503. The two clones lysed K562 cells expressing cognate HLA class allele(s), but not control K562 cells transfected with HLA-DR2b, confirming the above findings. The identification of four additional HLA alleles (DRB5*0101, DRB1*1101, B*3501 and B*3503) capable of presenting the P210b3a2 %%%fusion%%% region antigen will broaden the application of vaccine strategies for targeting CML cells.

1/7/3 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

16180508 PMID: 15507622

Secretion of a TNFR:Fc %%%fusion%%% protein following pulmonary administration of pseudotyped adeno-associated virus vectors.

Sandalon Ziv; Bruckheimer Elizabeth M; Lustig Kurt H; Rogers Linda C; Peluso Richard W; Burstein Haim

Targeted Genetics Corporation, 1100 Olive Way, Suite 100, Seattle, WA 98101-1844, USA.

Journal of virology (United States) Nov 2004, 78 (22) p12355-65, ISSN 0022-538X Journal Code: 0113724

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

This study evaluated and compared delivery of the tumor necrosis factor alpha receptor (TNFR)-immunoglobulin G1 (IgG1) Fc %%%fusion%%% (TNFR:Fc) gene to the lung by single and repeat administrations of multiple pseudotyped adeno-associated virus (AAV) vectors as a means for achieving systemic distribution of the soluble TNFR:Fc protein. A single endotracheal administration of AAV[2/5]cytomegalovirus (CMV)-TNFR:Fc vector (containing the %%%AAV2%%% inverted terminal repeats and AAV5 capsid) to the rat lung resulted in long-term, high levels of serum TNFR:Fc protein that gradually declined over a period of 8 months. Endotracheal delivery of AAV[2/1]CMV-TNFR:Fc resulted in serum TNFR:Fc protein levels that were detectable for at least 4 months but were 10-fold lower than that of the AAV[2/5] vector. In contrast, secretion of the TNFR:Fc protein following

pulmonary delivery of AAV[2/2]CMV-TNFR:Fc vector was very inefficient, and the protein was detected in the blood only when an airway epithelial cell-specific promoter, CC10, was substituted for the CMV enhancer/promoter to control transgene expression. In the context of AAV[2/5], the CC10 promoter was as efficient as CMV enhancer/promoter in generating similar levels of systemic TNFR:Fc protein, suggesting that this protein is secreted primarily from the airway epithelium. In mice, comparable long-term secretion of TNFR:Fc protein was demonstrated after AAV[2/2] and AAV[2/5] delivery, although the kinetics of transduction appeared to be different. All pseudotyped AAV vectors elicited serum anti-AAV capsid-neutralizing antibody responses, but these did not prevent lung transduction and efficient secretion of TNFR:Fc protein to the circulation following readministration with AAV[2/5]. These results highlight the potential utility of AAV vectors containing serotype 5 capsid to deliver and redeliver genes of secreted proteins to the lung to achieve long-term systemic protein expression.

Record Date Created: 20041027

Record Date Completed: 20041123

1/7/4 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13732280 PMID: 11262413

Binding of adeno-associated virus type 5 to 2,3-linked sialic acid is required for gene transfer.

Walters R W; Yi S M; Keshavjee S; Brown K E; Welsh M J; Chiorini J A; Zabner J

Departments of Internal Medicine, Physiology and Biophysics, and Otolaryngology, Howard Hughes Medical Institute, University of Iowa College of Medicine, Iowa City, Iowa 52242, USA.

Journal of biological chemistry (United States) Jun 8 2001, 276 (23) p20610-6, ISSN 0021-9258 Journal Code: 2985121R

Contract/Grant No.: T30DK54759; DK; NIDDK

Publishing Model Print-Electronic

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Recombinant adeno-associated viruses (AAV) are promising gene therapy vectors. Whereas AAV serotype 2-mediated gene transfer to muscle has partially replaced factor IX deficiency in hemophilia patients, its ability to mediate gene transfer to the lungs for cystic fibrosis is hindered by lack of apical receptors. However, AAV serotype 5 infects human airway epithelia from the lumenal surface. We found that in contrast to %%%AAV2%%% , the apical membrane of airway epithelia contains abundant high affinity receptors for AAV5. Binding and gene transfer with AAV5 was abolished by genetic or enzymatic removal of sialic acid from the cell surface. Furthermore, binding and gene transfer to airway epithelia was competed by lectins that specifically bind 2,3-linked sialic acid. These observations suggest that 2,3-linked sialic acid is either a receptor for AAV5 or it is a necessary component of a receptor complex. Further elucidation of the receptor for this virus should enhance understanding of parvovirus biology and expand the therapeutic targets for AAV vectors.

Record Date Created: 20010604

Record Date Completed: 20010712

Date of Electronic Publication: 20010321

1/7/5 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13545634 PMID: 10516053
Repeated delivery of adeno-associated virus vectors to the rabbit airway.
Beck S E; Jones L A; Chesnut K; Walsh S M; Reynolds T C; Carter B J; Askin F B; Flotte T R; Guggino W B
Eudowood Division of Pediatric Respiratory Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. sbeck@jhmi.edu
Journal of virology (UNITED STATES) Nov 1999, 73 (11) p9446-55, ISSN 0022-538X Journal Code: 0113724
Contract/Grant No.: PO1 HL51811; HL; NHLBI; PO1 HL51811-06; HL; NHLBI; RO1 DK51809; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Efficient local expression from recombinant adeno-associated virus (rAAV)-cystic fibrosis (CF) transmembrane conductance regulator (CFTR) vectors has been observed in the airways of rabbits and monkeys for up to 6 months following a single bronchoscopic delivery. However, it is likely that repeated administrations of rAAV vectors will be necessary for sustained correction of the CF defect in the airways. The current study was designed to test the feasibility of repeated airway delivery of rAAV vectors in the rabbit lung. After two doses of rAAV-CFTR to the airways, rabbits generated high titers of serum anti-AAV neutralizing antibodies. Rabbits then received a third dose of a rAAV vector containing the green fluorescent protein (GFP) reporter gene packaged in either AAV serotype 2 (%%%AAV2%%%) or serotype 3 (AAV3) capsids. Each dose consisted of 1 ml containing 5 x 10(9) DNase-resistant particles of rAAV vector, having no detectable replication-competent AAV or adenovirus. Three weeks later, GFP expression was observed in airway epithelial cells despite high anti-AAV neutralizing titers at the time of delivery. There was no significant difference in the efficiency of DNA transfer or expression between the rAAV3 and rAAV2 groups. No significant inflammatory responses to either repeated airway exposure to rAAV2-CFTR vectors or to GFP expression were observed. These experiments demonstrate that serum anti-AAV neutralizing antibody titers do not predict airway neutralization in vivo and that repeated airway delivery rAAV allows for safe and effective gene transfer.
Record Date Created: 19991104
Record Date Completed: 19991104

1/7/6 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13334283 PMID: 10196327
Adeno-associated virus (AAV) type 5 Rep protein cleaves a unique terminal resolution site compared with other AAV serotypes.
Chiorini J A; Afione S; Kotin R M
Molecular Hematology Branch, National Heart, Lung, and Blood Institute,

Bethesda, Maryland 20892, USA.
Journal of virology (UNITED STATES) May 1999, 73 (5) p4293-8, ISSN 0022-538X Journal Code: 0113724
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Adeno-associated virus (AAV) replication depends on two viral components for replication: the AAV nonstructural proteins (Rep) in trans, and inverted terminal repeat (ITR) sequences in cis. AAV type 5 (AAV5) is a distinct virus compared to the other cloned AAV serotypes. Whereas the Rep proteins and ITRs of other serotypes are interchangeable and can be used to produce recombinant viral particles of a different serotype, AAV5 Rep proteins cannot cross-complement in the packaging of a genome with an %%%AAV2%%% ITR. In vitro replication assays indicated that the block occurs at the level of replication instead of at viral assembly. %%%AAV2%%% and AAV5 Rep binding activities demonstrate similar affinities for either an %%%AAV2%%% or AAV5 ITR; however, comparison of terminal resolution site (TRS) endonuclease activities showed a difference in specificity for the two DNA sequences. %%%AAV2%%% Rep78 cleaved only a type 2 ITR DNA sequence, and AAV5 Rep78 cleaved only a type 5 probe efficiently. Mapping of the AAV5 ITR TRS identified a distinct cleavage site (AGTG TGGC) which is absent from the ITRs of other AAV serotypes. Comparison of the TRSs in the %%%AAV2%%% ITR, the AAV5 ITR, and the AAV chromosome 19 integration locus identified some conserved nucleotides downstream of the cleavage site but little homology upstream.

Record Date Created: 19990519
Record Date Completed: 19990519

? t s2/7/1-2

2/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0007666876 BIOSIS NO.: 199191049767
ADENO-ASSOCIATED VIRUS REP PROTEIN INHIBITS HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 PRODUCTION IN HUMAN CELLS
AUTHOR: ANTONI B A (Reprint); RABSON A B; MILLER I L; TREMPE J P; CHEJANOVSKY N; CARTER B J
AUTHOR ADDRESS: LABORATORY MOLECULAR CELLULAR BIOLOGY, ROOM 304, BUILDING 8, NATIONAL INSTITUTE DIABETES DIGESTIVE KIDNEY DISEASES, BETHESDA, MD 20892, USA**USA
JOURNAL: Journal of Virology 65 (1): p396-404 1991
ISSN: 0022-538X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The adeno-associated virus (AAV) rep gene encodes four proteins (Rep78, Rep68, Rep52, and Rep40) required for AAV DNA replication and AAV gene regulation. In addition, the Rep proteins may have pleiotropic regulatory effects in heterologous systems, and in particular Rep78 may mediate a negative regulatory effect. We analyzed the effects of the AAV rep gene on human immunodeficiency virus type 1 (HIV-1) gene expression. The rep gene proteins of AAV type 2 (%%%AAV2%%%) inhibited the

trans-activating ability of HIV-1. Constructs containing the %%%AAV2%%% rep gene (pHIVrep) or a CAT gene (pBennCAT) expressed from the 5' HIV-1 long terminal repeat were inducible for Rep78 and Rep68 or CAT expression, respectively, when cotransfected with a plasmid containing the HIV-1 %%%tat%%% gene (pARtat). When equivalent amounts of pHIVrep and pBennCAT were cotransfected with increasing amounts of pARtat, expression of CAT activity was decreased. The pHIVrep construct was more inhibitory than plasmids expressing rep from the wild-type %%%AAV2%%% p5 transcription promoter, rep expression from pHIVrep almost completely inhibited the replication of an HIV-1 proviral clone as measured by reversal transcriptase activity and p24 protein levels. Inhibition of HIV-1 production by Rep protein was also seen at the transcriptional level in that all HIV-1 transcripts were decreased when pHIVrep was present. The inhibitory effects of pHIVrep appear to be mediated primarily by Rep78 and perhaps Rep68. These results suggest that a trans-acting protein from a heterologous virus might be used to inhibit HIV-1 growth.

not of fusion

2/7/2 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09326630 PMID: 1845899

Adeno-associated virus Rep protein inhibits human immunodeficiency virus type 1 production in human cells.

Antoni B A; Rabson A B; Miller I L; Trempe J P; Chejanovsky N; Carter B J
Laboratory of Molecular and Cellular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland 20892.

Journal of virology (UNITED STATES) Jan 1991, 65 (1) p396-404, ISSN 0022-538X Journal Code: 0113724
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The adeno-associated virus (AAV) rep gene encodes four proteins (Rep78, Rep68, Rep52, and Rep40) required for AAV DNA replication and AAV gene regulation. In addition, the Rep proteins may have pleiotropic regulatory effects in heterologous systems, and in particular Rep78 may mediate a negative regulatory effect. We analyzed the effects of the AAV rep gene on human immunodeficiency virus type 1 (HIV-1) gene expression. The rep gene proteins of AAV type 2 (%%%AAV2%%%) inhibited the trans-activating ability of HIV-1. Constructs containing the %%%AAV2%%% rep gene (pHIVrep) or a CAT gene (pBennCAT) expressed from the 5' HIV-1 long terminal repeat were inducible for Rep78 and Rep68 or CAT expression, respectively, when cotransfected with a plasmid containing the HIV-1 %%%tat%%% gene (pARtat). When equivalent amounts of pHIVrep and pBennCAT were cotransfected with increasing amounts of pARtat, expression of CAT activity was decreased. The pHIVrep construct was more inhibitory than plasmids expressing rep from the wild-type %%%AAV2%%% p5 transcription promoter. rep expression from pHIVrep almost completely inhibited the replication of an HIV-1 proviral clone as measured by reverse transcriptase activity and p24 protein levels. Inhibition of HIV-1 production by Rep protein was also seen at the transcriptional level in that all HIV-1 transcripts were decreased when pHIVrep was present. The inhibitory effects of pHIVrep appear to be mediated primarily by Rep78 and perhaps Rep68. These results suggest that a

trans-acting protein from a heterologous virus might be used to inhibit HIV-1 growth.
Record Date Created: 19910207
Record Date Completed: 19910207
Enter P or PAGE for more
? t s5/7/1-2

5/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012058639 BIOSIS NO.: 199900318299
Recombinant adeno-associated virus (AAV) drives constitutive production of glutamate decarboxylase in neural cell lines
AUTHOR: Mi Jie; Chatterjee Saswati; %%%Wong Kamehameha K%%%; Forbes Chelsea ; Lawless George; Tobin Allan J (Reprint
AUTHOR ADDRESS: Brain Research Institute, UCLA, 695 E. Charles Young Drive South, Los Angeles, CA, 90095-1761, USA**USA
JOURNAL: Journal of Neuroscience Research 57 (1): p137-148 July 1, 1999 1999
MEDIUM: print
ISSN: 0360-4012
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Many neurological disorders result directly or indirectly from the loss of inhibitory function. Engineering the production of GABA, an inhibitory neurotransmitter, may therefore be able at least partly to restore the lost inhibition seen in epilepsy, Parkinson's disease, or Huntington's disease. In this article, we describe a set of recombinant adeno-associated viruses (AAVs) that can deliver cDNAs encoding the GABA-producing enzyme, glutamate decarboxylase (GAD), directly into neural cells. We have characterized these recombinant AAVs in several cell lines derived from the CNS. These recombinant AAVs effectively transduced all neural cell lines, although with different efficiencies. Transduction occurred in both proliferating and nonproliferating cells, but actively proliferating cell lines had approximately six times greater transduction efficiency than nonproliferating cells. Furthermore, these AAVs maintained long-term expression of GAD in an astrocytic cell line for at least sevenpassages. These recombinant AAVs are promising vehicles for investigating the potential therapeutic effects of GABA in animal models of epilepsy and neurodegenerative diseases.

5/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011033419 BIOSIS NO.: 199799667479
Cellular immunotherapy and autologous transplantation for hematologic malignancy
AUTHOR: Margolin Kim A; Negrin Robert S; %%%Wong Kamehameha K%%%; Chatterjee Saswati; Wright Christine; Forman Stephen J (Reprint
AUTHOR ADDRESS: Dep. Hematol. Bone Marrow Transplant., City Hope Natl. Med. Cent., 1500 E. Duarte Rd., Duarte, CA 91010, USA**USA
JOURNAL: Immunological Reviews 157 (0): p231-240 1997 1997

ISSN: 0105-2896
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Citation
LANGUAGE: English

? t s8/7/1-6

8/7/1 (Item 1 from file: 5)

0014712499 BIOSIS NO.: 200400078755
Identification of new MHC-restriction elements for presentation of the p210BCR-ABL %%%fusion%%% region to human cytotoxic T lymphocytes.
AUTHOR: Sun Ji-Yao; Senitzer David; Forman Stephen J; %%%Chatterjee%%% %%% Saswati%%%; Wong K K (Reprint
AUTHOR ADDRESS: Division of Hematology and Stem Cell Transplantation, City of Hope National Medical Center and Beckman Research Institute, Duarte, CA, 91010, USA**USA
AUTHOR E-MAIL ADDRESS: kkwong@coh.org
JOURNAL: Cancer Immunology Immunotherapy 52 (12): p761-770 December 2003 2003
MEDIUM: print
ISSN: 0340-7004
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Chronic myelogenous leukemia (CML) is characterized by a t(9;22) translocation resulting in expression of BCR-ABL %%%fusion%%% oncoproteins which are unique to the leukemic cells, necessary for oncogenesis, and potentially immunogenic. We have previously shown that human dendritic cells transduced with an %%%adeno%%%-associated virus vector encoding the %%%fusion%%% region of the b3a2 splice variant (p210b3a2) of the BCR-ABL oncoprotein elicit specific T-cell responses in vitro. Two cytotoxic T lymphocyte (CTL) clones generated in this fashion displayed restriction with previously unreported HLA alleles. The first, T1/B9, was CD4+ and restricted by DRB5*0101 (autologous) or DRB1*1101 (allogeneic). The minimum cytotoxic epitope (MCE) binding to DRB5*0101 for this clone was identified as FKQSSKALQ, overlapping the p210b3a2 %%%fusion%%% point (boldface). The MCE of DRB1*1101 for this clone differed from DRB5*0101, but also included the %%%fusion%%% point. The clonality of CTL T1/B9 was verified by analyses of TCRalpha/beta chain usage and DNA sequence analyses. To our knowledge, this is the first description of a single clone recognizing both DRB5*0101 and DRB1*1101. The other CTL clone, T1/33, was CD8+ and recognized HLA-B*3501 or B*3503 complexed with an MCE, RPVASDFEP, derived from the c-abl sequence in proximity to the p210b3a2 %%%fusion%%% point. K562 cells transfected with plasmids encoding HLA-DRA +B5*0101, B*3501, or B*3503 but not controls expressing DRA+DRB1*1501 were lysed by cognate CTL clones, confirming that DRB5*0101 and B*3501/3 could present p210b3a2 joining region epitopes via endogenous processing. The identification of three additional HLA alleles (DRB5*0101, B*3501, and B*3503) presenting the p210b3a2 %%%fusion%%%-region antigen will broaden the application of vaccine strategies for targeting CML cells. The findings of single CTL clones cross-recognizing autologous (DRB5*0101 or B*3501) and allogeneic (DRB1*1101 or B*3503) HLA alleles presenting BCR-ABL %%%fusion%%%-region

epitopes implies the potential separation of graft-versus-leukemia from graft-versus-host effects.

8/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013770219 BIOSIS NO.: 200200363730
Immunogenicity of a p210BCR-ABL %%%fusion%%% domain candidate DNA vaccine targeted to dendritic cells by a recombinant %%%adeno%%%-associated virus vector in vitro
AUTHOR: Sun Ji-Yao; Krouse Robert S; Forman Stephen J; Senitzer David; Sniecinski Irena; %%%Chatterjee Saswati%%%; Wong K K Jr (Reprint
AUTHOR ADDRESS: Division of Hematology and Stem Cell Transplantation, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA, 91010, USA**USA
JOURNAL: Cancer Research 62 (11): p3175-3183 June 11, 2002 2002
MEDIUM: print
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Chronic myelogenous leukemia (CML) is characterized by a t(9;22) translocation, which results in the expression of chimeric BCR-ABL %%%fusion%%% oncoproteins that are necessary for oncogenesis, unique to the leukemic clones, and represent enticing targets for immunotherapy. As a strategy for the immunotherapy of CML, we constructed a recombinant %%%adeno%%%-associated virus vector encoding the p210BCR-ABL b3a2 variant %%%fusion%%% region with flanking sequences (CWRBA) and used it to express the BCR-ABL %%%fusion%%% region within primary human dendritic cells (DCs), the most potent antigen-presenting cells currently known. Peripheral blood mononuclear cells from healthy donors were primed and restimulated in vitro with autologous DCs transduced with purified CWRBA, CWRAP (negative control), or pulsed with a peptide corresponding to the %%%fusion%%% domain (positive control). No specific responses were generated using DCs transduced with CWRAP. In contrast, CWRBA-transduced DCs primed autologous T cells in an antigen-specific, MHC-restricted fashion to levels comparable with the positive control. CWRBA-transduced DCs elicited both cytotoxic CD4+/Th1 and CD8+ responses, although the former were more readily detected in this system. Cytotoxicity against a tumor cell line endogenously expressing the p210BCR-ABL b3a2 variant %%%fusion%%% region was also demonstrable. In addition, HLA-DRB5*0101+DRA (DR2a) was identified as a new restriction element capable of presenting the b3a2 BCR-ABL %%%fusion%%% region epitope. Thus, the construct developed herein may serve as a candidate vaccine for gene-based antigen-specific immunotherapy of CML and may serve as a paradigm for the use of DCs transduced with recombinant %%%adeno%%%-associated virus vectors encoding multiepitope immunogens for vaccine development.

8/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013605117 BIOSIS NO.: 200200198628

Development of a P210BCR-ABL %%%fusion%%% domain candidate dendritic cell DNA vaccine

AUTHOR: Sun Ji-Yao (Reprint); %%%Chatterjee Saswati%%%; Forman Stephen J (Reprint); Senitzer David (Reprint); Wong K K Jr (Reprint
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JOURNAL: Blood 98 (11 Part 1): p236a November 16, 2001 2001
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ISSN: 0006-4971
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Chronic myelogenous leukemia (CML) is characterized by a t(9;22) translocation which results in the expression of chimeric BCR-ABL %%%fusion%%% oncoproteins that are necessary for oncogenesis, unique to the leukemic clones, and represent enticing targets for immunotherapy. Furthermore, of hematological malignancies, the protective role of host immune responses has been most convincingly demonstrated for CML. Thus, methods to exploit and specifically enhance these responses could reduce the risk of relapse following hematopoietic stem cell transplantation for CML. As a strategy to augment anti-leukemic immune responses, we developed a candidate DNA vaccine based on recombinant %%%adeno%%% -associated virus (rAAV) vectors which targets the P210BCR-ABL %%%fusion%%% region. We previously demonstrated that primary human dendritic cells (DCs), the most potent antigen presenting cells currently known, could be transduce with rAAV vectors. An 835 bp cDNA fragment containing the P210BCR-ABL b3a2 variant (P210b3a2) %%%fusion%%% domain and flanking sequences was inserted into an rAAV vector under control of the RSV promoter, yielding pCWRF8. 293 cells transfected with pCWRF8 expressed an appropriate transcript, as well as the predicted 25 KDa truncated protein. Using an institutionally approved protocol, PBMCs from healthy donors were primed and restimulated in vitro with autologous DCs transduced with vCWRF8 (DC/F8), vCWRAP, an equivalent control vector encoding human placental alkaline phosphatase (hu-PLAP)(DC/AP, negative control), or pulsed with a 25-amino acid peptide (Pb3) corresponding to the p210b3a2 %%%fusion%%% domain (DC/b3, positive control). No specific responses were generated using DC/AP, the negative transduction control. In contrast, BCR-ABL vector transduced DC were capable of priming autologous T cells to an equivalent extent to BCR-ABL peptide pulsed DC, the positive control. Proliferative responses were demonstrable in four donors with MHC alleles previously described in the literature as capable of responding to the BCR-ABL %%%fusion%%% domain, but not in two donors with divergent alleles. In addition, CTL clones were identified that specifically lysed BCR-ABL peptide pulsed autologous B-lymphoid cell lines, but not control cells pulsed with irrelevant peptides. To determine whether the CTL clones recognize CML cells, K562 cells, a leukemic cell line expressing the BCR-ABL P210b3a2 were engineered to express a variety of HLA alleles. CTL clones specifically lysed K562 cells expressing identical HLA alleles, confirming that responses were endogenous tumor antigen specific and MHC restricted. Although both CD4+ and CD8+ CTL directed against BCR-ABL epitopes could be generated in this system, CD4+ clones were more readily identified, implying that the frequency of CD4+ T-cell precursor anti-BCR-ABL was higher. Thus, the

construct developed herein may serve as an important candidate for gene-based immunotherapy of CML.

8/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013559564 BIOSIS NO.: 200200153075
Identification of new MHC restriction elements for presentation of the p210 BCR-ABL %%%fusion%%% region to human cytotoxic T lymphocytes (CTL)
AUTHOR: Sun Ji-Yao (Reprint); %%%Chatterjee Saswati%%%; Forman Stephen J (Reprint); Senitzer David (Reprint); Wong K K Jr (Reprint
AUTHOR ADDRESS: Division of Hematology and Bone Marrow Transplantation, National Medical Center, City of Hope, Duarte, CA, USA**USA
JOURNAL: Blood 98 (11 Part 1): p147a November 16, 2001 2001
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SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Chronic myelogenous leukemia (CML) is characterized by a t(9;22) translocation which results in the expression of chimeric, %%%fusion%%% transcripts consisting of cellular bcr and abl genes. BCR-ABL %%%fusion%%% transcripts and corresponding oncoproteins are both necessary for oncogenesis, and are unique to the leukemic cells. Furthermore, the BCR-ABL oncogene %%%fusion%%% region is immunogenic, and several HLA class I and II alleles can present %%%fusion%%% region epitopes to T lymphocytes, generating interest in the potential for the development of CML specific vaccines. Here we report four additional HLA alleles which present %%%fusion%%% region epitopes of the b3a2 splice variant (P210b3a2) of the BCR-ABL oncogene. To elicit anti-BCR-ABL T-cell responses, our studies employed primary human dendritic cells (DC) transduced with a recombinant %%%adeno%%%-associated virus (AAV2) vector encoding a truncated P210b3a2 cDNA fragment containing the %%%fusion%%% region. Two CTL clones generated in this fashion displayed restriction with previously undescribed HLA alleles. The first CTL clone was CD4+ and of the Th1 functional phenotype. Screening a panel of 10 HLA divergent antigen presenting cell lines demonstrated that this clone was HLA-DRB5*0101 (DR2a) restricted; findings confirmed by anti-HLA-DR monoclonal antibody blocking experiments and demonstration of antigen specific recognition of a cell line into which HLA-DRA and DRB5*0101 were introduced. The minimum cytotoxic epitope (MCE) of the P210b3a2 %%%fusion%%% region binding to DR2a for this clone was identified as FKQSSKALQ, the bolded K representing the new amino acid in the P210b3a2 junction region. Interestingly, this clone could also recognize cells expressing HLA-DRB1*1101 pulsed with a P210b3a2 %%%fusion%%% region peptide. The MCE binding to HLA-DRB1*1101 molecule for this clone is different from FKQSSKALQ. We believe that this is the first description of a single clone recognizing HLA-DRB5*0101 and DRB1*1101. The other BCR-ABL specific CTL clone was CD8+ and HLA-B*3501 and B*3503 restricted, findings similar to those reported by Khanna et al who described a CTL clone that recognized an Epstein Barr virus epitope presented by both

B*3501 and B*3503 (Eur J Immunol 1999; 29:1587). To determine whether HLA-DR2a and B35 could present P210b3a2 joining region epitopes via endogenous processing, K562 cells, a leukemic cell line expressing P210b3a2, were transfected with expression plasmids encoding HLA-DR2a, B*3501 or B3503. The two clones lysed K562 cells expressing cognate HLA class allele(s), but not control K562 cells transfected with HLA-DR2b, confirming the above findings. The identification of four additional HLA alleles (DRB5*0101, DRB1*1101, B*3501 and B*3503) capable of presenting the P210b3a2 %%%fusion%%% region antigen will broaden the application of vaccine strategies for targeting CML cells.

8/7/5 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15063303 PMID: 14564482

Identification of new MHC-restriction elements for presentation of the p210(BCR-ABL) %%%fusion%%% region to human cytotoxic T lymphocytes.

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Cancer immunology, immunotherapy - CII (Germany) Dec 2003, 52 (12) p761-70, ISSN 0340-7004 Journal Code: 8605732

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Chronic myelogenous leukemia (CML) is characterized by a t(9;22) translocation resulting in expression of BCR-ABL %%%fusion%%% oncoproteins which are unique to the leukemic cells, necessary for oncogenesis, and potentially immunogenic. We have previously shown that human dendritic cells transduced with an %%%adeno%%%-associated virus vector encoding the %%%fusion%%% region of the b3a2 splice variant (p210(b3a2)) of the BCR-ABL oncoprotein elicit specific T-cell responses in vitro. Two cytotoxic T lymphocyte (CTL) clones generated in this fashion displayed restriction with previously unreported HLA alleles. The first, T1/B9, was CD4(+) and restricted by DRB5*0101 (autologous) or DRB1*1101 (allogeneic). The minimum cytotoxic epitope (MCE) binding to DRB5*0101 for this clone was identified as FKQSSKALQ, overlapping the p210(b3a2) %%%fusion%%% point (boldface). The MCE of DRB1*1101 for this clone differed from DRB5*0101, but also included the %%%fusion%%% point. The clonality of CTL T1/B9 was verified by analyses of TCRalpha/beta chain usage and DNA sequence analyses. To our knowledge, this is the first description of a single clone recognizing both DRB5*0101 and DRB1*1101. The other CTL clone, T1/33, was CD8+ and recognized HLA-B*3501 or B*3503 complexed with an MCE, RPVASDFEP, derived from the c-abl sequence in proximity to the p210(b3a2) %%%fusion%%% point. K562 cells transfected with plasmids encoding HLA-DRA + B5*0101, B*3501, or B*3503 but not controls expressing DRA + DRB1*1501 were lysed by cognate CTL clones, confirming that DRB5*0101 and B*3501/3 could present p210(b3a2) joining region epitopes via endogenous processing. The identification of three additional HLA alleles (DRB5*0101, B*3501, and B*3503) presenting the

p210(b3a2) %%%fusion%%% -region antigen will broaden the application of vaccine strategies for targeting CML cells. The findings of single CTL clones cross-recognizing autologous (DRB5*0101 or B*3501) and allogeneic (DRB1*1101 or B*3503) HLA alleles presenting BCR-ABL %%%fusion%%%-region epitopes implies the potential separation of graft-versus-leukemia from graft-versus-host effects.

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8/7/6 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14234298 PMID: 12036931

Immunogenicity of a p210(BCR-ABL) %%%fusion%%% domain candidate DNA vaccine targeted to dendritic cells by a recombinant %%%adeno%%%-associated virus vector in vitro.

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Cancer research (United States) Jun 1 2002, 62 (11) p3175-83, ISSN 0008-5472 Journal Code: 2984705R

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Document type: Journal Article
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Chronic myelogenous leukemia (CML) is characterized by a t(9;22) translocation, which results in the expression of chimeric BCR-ABL %%%fusion%%% oncoproteins that are necessary for oncogenesis, unique to the leukemic clones, and represent enticing targets for immunotherapy. As a strategy for the immunotherapy of CML, we constructed a recombinant %%%adeno%%%-associated virus vector encoding the p210(BCR-ABL) b3a2 variant %%%fusion%%% region with flanking sequences (CWRBA) and used it to express the BCR-ABL %%%fusion%%% region within primary human dendritic cells (DCs), the most potent antigen-presenting cells currently known. Peripheral blood mononuclear cells from healthy donors were primed and restimulated in vitro with autologous DCs transduced with purified CWRBA, CWRAP (negative control), or pulsed with a peptide corresponding to the %%%fusion%%% domain (positive control). No specific responses were generated using DCs transduced with CWRAP. In contrast, CWRBA-transduced DCs primed autologous T cells in an antigen-specific, MHC-restricted fashion to levels comparable with the positive control. CWRBA-transduced DCs elicited both cytotoxic CD4+/Th1 and CD8+ responses, although the former were more readily detected in this system. Cytotoxicity against a tumor cell line endogenously expressing the p210(BCR-ABL) b3a2 variant %%%fusion%%% region was also demonstrable. In addition, HLA-DRB5(*)0101+DRA (DR2a) was identified as a new restriction element capable of presenting the b3a2 BCR-ABL %%%fusion%%% region epitope. Thus, the construct developed herein may serve as a candidate vaccine for gene-based antigen-specific immunotherapy of CML and may serve as a paradigm for the use of DCs transduced with recombinant %%%adeno%%% -associated virus vectors encoding multiepitope immunogens for

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vaccine development.
  Record Date Created: 20020530
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